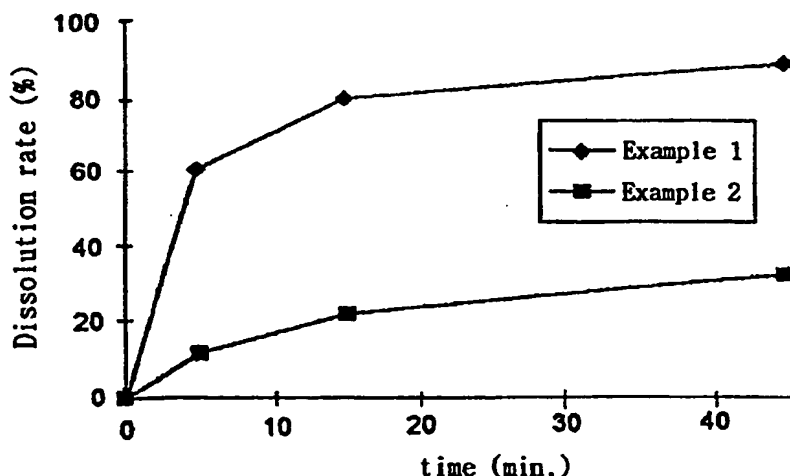




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/545		A1	(11) International Publication Number: WO 99/44614
			(43) International Publication Date: 10 September 1999 (10.09.99)
(21) International Application Number: PCT/KR99/00095		#101-1511, 87-1, Noyou 2-dong, Kwangjin-ku, Seoul 143-302 (KR).	
(22) International Filing Date: 3 March 1999 (03.03.99)		(74) Agents: CHOI, Kyu, Pal et al.; 824-20, Yeoksam-dong, Kangnam-ku, Seoul 135-080 (KR).	
(30) Priority Data: 1998/6866 3 March 1998 (03.03.98) KR 1998/33463 18 August 1998 (18.08.98) KR		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): DAEWOONG PHARMACEUTICAL CO., LTD. [KR/KR]; 223-23, Sangdaewon-dong, Joongwon-ku, Sungnam-city, Kyunggi-do 462-120 (KR).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): CHUNG, Jong, Keun [KR/KR]; Moogoonghwa Apartment, #122-1801, Keumjeong-dong, Kunpo-shi, Kyunggi-do 435-050 (KR). KIM, Hak, Hyoung [KR/KR]; Sansung Apartment, 103-1702, Sangdaewon 1-dong, Joongwon-ku, Sungnam-shi, Kyunggi-do 462-121 (KR). LIM, Sang, Hee [KR/KR]; Shinheung Joogong Apartment, #107-1411, Shinheung 2-dong, Soojeong-ku, Sungnam-shi, Kyunggi-do 461-162 (KR). PARK, Jeong, Hwa [KR/KR]; Chungshil Apartment, #6-701, Daechi-dong, Kangnam-ku, Seoul 135-280 (KR). PARK, Joon, Woo [KR/KR]; Hangang Woosung Apartment		Published With international search report.	

(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING CEFUROXIME AXETIL STABLE FOR MOISTURE ABSORPTION



(57) Abstract

The present invention relates to a pharmaceutical composition containing cefuroxime axetil wherein the active ingredient is not gelled by moisture absorption and is thus stable during storage period. More specifically, the present invention relates to a pharmaceutical composition which comprises amorphous cefuroxime axetil as an active ingredient and silicon dioxide or its hydrate as a micro-environmental pH adjuster and an anti-gelling agent for cefuroxime axetil. The composition according to the present invention can be provided in the oral formulation such as tablets, capsules, granules, powders and dry syrups.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

- 1 -

PHARMACEUTICAL COMPOSITION CONTAINING CEFUROXIME AXETIL STABLE FOR MOISTURE ABSORPTION

TECHNICAL FIELD

5

The present invention relates to a pharmaceutical composition containing cefuroxime axetil. More specifically, the present invention relates to a pharmaceutical composition which comprises amorphous cefuroxime axetil as an active ingredient and silicon dioxide or its hydrate as a micro-environmental pH adjustor around cefuroxime
10 axetil and an anti-gelling agent for cefuroxime axetil.

BACKGROUND ART

Cefuroxime is an antibiotic showing a broad anti-bacterial activity spectrum
15 against gram-positive and gram-negative bacteria as disclosed in UK Patent No. 1,453,049. Cefuroxime and its salts have been generally administered as an injectable preparation because they are insufficiently absorbed from the gastrointestinal tract.

As an effort to solve the problem involved with the administration of cefuroxime
20 into the body, cefuroxime axetil was developed as a prodrug which can be administered via oral route. Cefuroxime axetil is an ester derivative of cefuroxime in which 4-carboxylic group of cefuroxime is esterified with 1-acetoxyethyl group. As described in UK Patent No. 1,571,683, if 1-acetoxyethyl ester group exists in cefuroxime, the ester derivative can be administered via oral route because the lipophilicity of
25 cefuroxime is increased and thus, the absorption of the drug from the gastrointestinal tract is increased. After being administered by oral route, cefuroxime axetil is rapidly hydrolyzed by non-specific esterases present in the intestinal mucosa and blood within the body to exert the pharmacological effect as a drug, cefuroxime. It is especially advantageous to use cefuroxime axetil in an amorphous form as described in UK Patent
30 No. 2,127,401.

- 2 -

However, since cefuroxime axetil has a strong bitter taste which cannot be easily masked, an appropriate mean to mask the bitter taste is required in order to formulate it for oral administration. When formulating an active ingredient with a bitter taste into tablets, the method for masking the bitter taste generally used in the art is to coat tablet with a film. However, as described in Korean Patent No. 73572, there are drawbacks that if cefuroxime axetil contacts aqueous medium, a mass of gelatin shape is produced and, when it is administered in the form of a film coated tablet, cefuroxime axetil contained in the tablet core is gelled even if gastric juice is relatively slowly penetrated into the tablet core through the film, thereby resulting in insufficient absorption. Due to such a gel formation, the tablet core is insufficiently disintegrated and thus, the dissolution of the cefuroxime axetil is lowered. Therefore, it was impossible to provide the desired pharmacological effect because the absorption of the drug into the gastrointestinal tract is considerably decreased.

In order to solve these drawbacks, a cefuroxime axetil tablet comprising a film which can be rapidly ruptured in 0.07 M of aqueous hydrochloric acid solution and a tablet core which is disintegrated immediately after the film is ruptured was developed. [See, Korean Patent No.73572]. This method can be said as the one which the problem of gel formation is overcome and high bioavailability is maintained by a film coated tablet in which, upon contact with gastrointestinal juice, the film coating ruptures very rapidly and the core then immediately disintegrates, thereby allowing dispersion and dissolution of cefuroxime axetil in the gastrointestinal tract before gel formation.

However, the thin film coated with the water soluble film forming material cannot completely block the effect by outer environment. That is, moisture in air is permeated into the core of tablets upon storage and as a result, the cefuroxime axetil is gelled within the core of the tablet giving poor dissolution. Therefore, there is a serious problem that dissolution rate of the core is decreased from the gastro-intestinal tract and the bioavailability of cefuroxime axetil is also decreased.

The foregoing can be found from the fact that if cefuroxime axetil tablet is stored in a brown glass bottle in an opened state under the accelerated condition of 40 °C, and 75% of relative humidity, the moisture content is increased by 2 - 3 % even after the time lapse of one month and it takes more than 60 minutes for the tablet to be disintegrated [See, a Japanese journal of "Antibiotics & Chemotherapy", Vol 7, No. 11, 1991]. Further, the present inventors have confirmed that an undissolved mass was frequently remained even after 45 minutes when subjecting the tablet prepared by the above method to the dissolution test method as described in the monograph of the cefuroxime axetil tablets of Vol. 23, page 316 of the U.S. Pharmacopeia. Due to this mass, the drug is not completely dissolved and the bioavailability is decreased. Therefore, the method whereby the film is rapidly ruptured and the tablet core is immediately disintegrated using the water soluble film forming material as disclosed in Korean Patent No. 73572 may be effective in the prevention of gelation of the cefuroxime axetil by gastric juice and in increasing the dissolution rate upon administration to the patient, thereby improving the bioavailability in a very short period of storage. However, the preparation according to said method still has a problem that it cannot completely block the absorption of moisture into the core upon long term storage and thus rather may cause gelation of the active ingredient within the core of the tablet upon storage.

20

As an effort to prevent the gelation of the cefuroxime axetil particles, Korean Patent Publication No. 95-9097 discloses a method for preparing a cefuroxime axetil-containing composition in a finely divided particle form coated with lipid which is water-insoluble, masks bitter taste and is dispersed readily upon contact with gastric juice.

25

However, the above method has drawbacks that it must use cefuroxime axetil having the particle size less than 250 μm and should employ a complicated coating process in order to assure the prevention of the absorption of moisture. Therefore, this method is also inconvenient for preparing solid formulation of cefuroxime axetil for oral administration.

30

DISCLOSURE OF THE INVENTION

It is therefore an object of the present invention to provide a pharmaceutical composition in which the above problems were eliminated or remarkably improved.

5

Another object of the present invention is to provide a pharmaceutical composition which comprises amorphous cefuroxime axetil as an active ingredient and silicon dioxide or its hydrate as a micro-environmental pH adjustor around cefuroxime axetil and an anti-gelling agent for cefuroxime axetil.

10

Still another object of the present invention is to provide a pharmaceutical composition in an oral formulation such as tablet, capsule, granule, powder and dry syrup.

15 Further objects and advantages of the invention will become apparent through reading the remainder of the specification.

The foregoing has outlined some of the more pertinent objects of the present invention. These objects should be construed to be merely illustrative of some of the
20 more pertinent features of the invention. Many other beneficial results can be obtained by applying the disclosed invention in a different manner or by modifying the invention within the scope of the disclosure. Accordingly, other objects and a more thorough understanding of the invention may be found by referring to the detailed description of the preferred embodiment in addition to the scope of the invention defined by the
25 claims.

The present inventors have conducted an extensive research for many years in order to develop a stable oral preparation wherein the gel formation of cefuroxime axetil which may occur upon storage can be effectively prevented by employing a
30 simple process that does not require the complicated coating process as mentioned in connection with the above Korean patent. As a result, the inventors have surprisingly

- 5 -

discovered that when a composition, in which silicon dioxide or its hydrate serving as a micro-environmental pH adjustor near cefuroxime axetil and an anti-gelling agent for cefuroxime axetil is mixed with cefuroxime axetil, is provided as an oral formulation, silicon dioxide or its hydrate completely prevented the degradation or gel formation of cefuroxime axetil due to absorption of moisture in air and the gel formation of cefuroxime axetil by the permeation of the gastric juice into the tablet core upon administration and make it possible to increase the dissolution rate upon administration to the patient, thereby improving the bioavailability, and have completed the present invention.

10

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 is a graph according to the result of Experiment 1 showing the dissolution rate of cefuroxime axetil tablet cores of Examples 1 and 2 (- ♦ -: Tablet core of Example 1 containing silicon dioxide, - ■ -: Tablet core of Example 2 without silicon dioxide).

Fig. 2 is a graph according to the result of Experiment 2 showing the dissolution rate of the cefuroxime axetil capsules in Examples 3 and 4 (- ♦ -: Capsule of Example 3 containing silicon dioxide, - ■ -: Capsule of Example 4 without silicon dioxide).

Fig. 3 is a graph according to the result of Experiment 4 showing the dissolution rate of cefuroxime axetil tablet in Example 5 (test preparation) compared with that of the product according to Korean Patent No. 73572 (- ■ -: Test preparation, - ♦ -: Comparative preparation).

Fig. 4 is a graph according to the result of Experiment 5 showing the dissolution rate after 45 minutes of cefuroxime axetil tablet in Example 5 compared with that of the commercial product (- □ -: Tablet of Example 5, - ■ -: Commercial Product).

BEST MODE FOR CARRYING OUT THE INVENTION

Hereinafter, the invention will be illustrated in more detail.

5 In an aspect, the present invention provides a pharmaceutical composition which comprises amorphous cefuroxime axetil as an active ingredient and silicon dioxide or its hydrate as a micro-environmental pH adjustor around cefuroxime axetil and an anti-gelling agent for cefuroxime axetil.

10 The present invention, in an another aspect, provides the above composition in an oral formulation such as tablet, capsule, granule, powder and dry syrup.

 The composition according to the present invention, especially in the oral formulation such as tablet, capsule, granule, powder and dry syrup does not raise any
15 problems involved in the prior art such as, for example, the degradation or gel formation of the cefuroxime axetil due to the absorption of moisture in air and the gel formation of cefuroxime axetil by the gastric juice upon administration and make it possible to increase the dissolution rate upon administration into patients, thereby improving the bioavailability.

20 As for an excipient to be suitably used in inhibiting the gelation of a drug which is susceptible to the gelation, it is important that the attractive force between each of the particles of the drug should be minimized and the particles of drug should be evenly dispersed into the dispersion medium. Hitherto, it was general to admix the
25 drug with a disintegrant which can be well combined with the drug and has large disintegrating power to disperse the particles. However, if the conventional disintegrants are used, the gel formation of cefuroxime axetil by the absorption of moisture in air was not effectively prevented.

30 The composition according to the present invention contains silicon dioxide or its hydrate as a micro-environmental pH adjustor and an anti-gelling agent for

cefuroxime axetil. According to the experiments by the present inventors, it was found that the hydrate form of silicon dioxide also showed the similar effect to silicon dioxide. Therefore, it is understood that even unless specifically indicated, the hydrate form of silicon dioxide is encompassed into silicon dioxide.

5

Silicon dioxide is an excipient which can be commonly used in the medicinal composition as a flow aid or a suspending agent due to its excellent fluidity and dispersity. The amount of the disintegrant which is generally used in the drug formulation in the art is within a range between 0.1% and 0.5% by weight. The
10 excipient is also used as an adsorbent due to its broad surface area compared with other excipients.

Hitherto, silicon dioxide or its hydrate has not been used for the purpose of preventing gel formation in the cefuroxime axetil composition. As an example, the
15 prevention of gel formation in the cefuroxime axetil film-coated tablet disclosed in KR Patent No. 73572 is made by disintegrant which is generally used in the art. In the above patent, silicon dioxide is used as lubricants and flow aids. Further, the trace amount of less than about 0.25 % by weight was used for the tablet. Therefore, it is apparent that the use of silicon dioxide is remarkably differentiated from the KR Patent
20 No.73572 in aspects of the purpose and the mixing ratio, and thus, the KR patent never teaches the use of silicon dioxide as a anti-gelling agent for the cefuroxime axetil composition.

The mixing ratio of cefuroxime axetil with silicon dioxide or its hydrate used
25 in the present invention in order to prevent gelation of cefuroxime axetil is not limited to a specific ratio, but is preferable to be used within the ratio between 1:0.1 - 1:1 by weight, with the ratio between 1:0.25 - 1:0.35 by weight being most preferable. If the amount of silicon dioxide is below 1:0.1 weight ratio, the gel formation of cefuroxime axetil cannot be sufficiently prevented. If the amount is larger than 1:1 weight ratio,
30 a problem in the preparation process such as a difficulty in the tableting process may arise.

The mixing of cefuroxime axetil and silicon dioxide or its hydrate is carried out in a conventional manner well known in the art with the conventional mixer.

Since silicon dioxide or its hydrate has an excellent fluidity, a high miscibility
5 with cefuroxime axetil can be obtained. Even if relatively small amount of silicon dioxide is mixed with cefuroxime axetil, the particles of silicon dioxide are evenly distributed between the particles of cefuroxime axetil due to the broad surface area of silicon dioxide, thereby the attractive force between particles of cefuroxime axetil being reduced to eliminate electric charge and the occurrence of gelation of cefuroxime axetil
10 being subsequently prevented.

Therefore, when an oral formulation prepared from the composition comprising a specific amount of silicon dioxide or its hydrate and an effective amount of cefuroxime axetil is administered into a patient, sufficient dissolution is made since the
15 gel formation of cefuroxime axetil does not occur even if the rupture of a film is not rapidly proceeded, and in addition, gel formation is not occur even if moisture in air is absorbed into the formulation upon storage.

In addition, cefuroxime axetil reveals the lowest hydrolysis rate in the pH
20 range between 3.5 and 5.5 (See, Pharmaceutical Research, Vol. 8, No. 7, 1991, p896).

In pH > 5.5, the decomposition rate of cefuroxime axetil increases (See, the Japanese journal of "Antibiotics & Chemotherapy", Vol. 7, No. 11, 1991). Therefore, when considering the stability of cefuroxime axetil in the micro-environment within the preparation, it is preferable that aqueous pH of the excipient be preferably a range
25 between 3.5 and 5.5. Since a 4% aqueous suspension of silicon dioxide or its hydrate has pH values between 3.5 and 4.4, if cefuroxime axetil is mixed with silicon dioxide to prepare solid formulation for oral administration, the micro-environment around cefuroxime axetil is maintained with an acidic state between 3.5 and 5.5 to increase the stability of cefuroxime axetil. Therefore, silicon dioxide or its hydrate
30 meets the acidic state requirement of tablet core of cefuroxime axetil.

The amount of silicon dioxide or its hydrate used in the composition of the invention is preferably 8 to 45% by weight based on the solid formulation. It is more preferable to use silicon dioxide or its hydrate in an amount of 10 to 20% by weight.

5 Cefuroxime axetil in the composition of the present invention is preferably used in an amount within the range from 50 mg to 500 mg based on cefuroxime per unit dose. Dose of cefuroxime axetil for adults will typically be 100 to 3,000 mg/day as cefuroxime and 125 to 1,000 mg/day for children by dividing it into two or more times per day, if necessary, although the precise dose may depend on the conditions of
10 disease to be treated, the age and the severity of a patient and the frequency of administration.

The composition according to the present invention may be prepared in the oral formulation with the conventional pharmaceutical excipients, such as, for example, a
15 disintegrant, a binder, a colorant, a solubilizer, a sweetener, a flavor, etc. Such oral formulation includes tablet, capsule, granule, powder and dry syrup, etc.

When cefuroxime axetil containing composition is prepared in a tablet formulation, it is preferable that the mixing ratio of cefuroxime axetil and silicon
20 dioxide or its hydrate is within a range from 1:0.1 to 1:1 by weight. The composition may be contained in an amount of 16 to 90% by weight based on the tablet, with the range from 20 to 80% by weight being more preferable. It is preferable that a unit tablet contain cefuroxime axetil in an amount of the range from 50 to 500 mg.

25 A disintegrating agent may be added to the tablet in order to increase the dissolution rate by increasing the disintegrating rate of the tablet core of cefuroxime axetil. Examples of the excipient which may be desirably added include sodium starch glycolate, polacrillin potassium, low-substituted hydroxypropyl cellulose, etc.

30 The term, "low-substituted hydroxypropyl cellulose" used herein is defined as cellulose which contains not less than 5.0 percent and not more than 16 percent of

hydroxy-propoxy group (-OCH₂CHOHCH₃).

In addition, the surface of tablet according to the invention may be film-coated with a film forming material in order to mask the bitter taste and to prevent moisture
5 from penetrating into the tablet core.

In the present invention, as the film forming material, a polymeric material can be used without limitation, provided that it has a tight molecular structure and preferably has a molecular weight above 20,000 and more preferably can not be easily
10 dissolved in an aqueous solution. The term "film coating material" or "film forming material" in the present invention can be interchangeably used with a term, "film substrate".

Furthermore, when considering the decomposition rate of cefuroxime axetil
15 according to pH, it is most preferable for the film forming material to have acidic nature in an aqueous solution. That is, it is possible to enhance the stability of cefuroxime axetil by film-coating the surrounding of the tablet core with a polymeric material having an acidic nature to make pH of the micro-environment of cefuroxime axetil near 3.5 - 5.5 wherein the decomposition rate of cefuroxime axetil is the lowest.
20 The film substrate used in the prior art, Korean Patent No. 73572, is a polymeric material of a neutral nature in an aqueous solution. However, this may provoke a serious problem to the stability of active ingredient by making the pH of the micro-environment of cefuroxime axetil neutral or above neutral.

25 Acid polymer which can be used as the film substrate in the present invention includes such as, for example, methacrylic copolymer (i.e., Eudragit L, Eudragit S, etc.), hydroxy propylmethylcellulose phthalate, cellulose acetate phthalate, hydroxypropylmethyl cellulose acetate succinate, polyvinyl alcohol, etc. The polymeric material can be used in combination of two or more materials based on the
30 nature of each material. This may be used in combination with other water soluble polymer materials in the film coating of the tablet core of cefuroxime axetil.

The film forming material may contain one or more excipients which are conventionally added to the film substrate, examples of which are a plasticizer, a preservatives, a colorant, a sunscreen, etc. These excipients make the coating process smooth and improve the nature and shape of the film. The amount to apply the film forming material may vary depending upon the nature of each film substrate and can be determined by taking into consideration the stability and the dissolution rate of cefuroxime axetil. The thickness of the film may be various since the tablet according to the present invention shows good dissolution rate regardless of the rupture rate of film.

10

It is also possible to present cefuroxime axetil-containing composition in the form of a capsule.

When cefuroxime axetil containing composition is prepared in a capsule formulation, it is preferable that the mixing ratio of cefuroxime axetil and silicon dioxide or its hydrate is 1:0.1 to 1:1 by weight. The composition may be contained in an amount of 16 to 90% by weight based on the capsule, with the range from 20 to 80% by weight being more preferable. It is preferable that a unit capsule contain cefuroxime axetil in the range from 50 to 500 mg as cefuroxime.

20

Other excipients may be added into the capsule formulation. A disintegrant may be added to the capsule in order to increase the dissolution rate by increasing the disintegrating rate of the capsule. Examples of the excipient which may be desirably added include sodium starch glycolate, polacrillin potassium, low-substituted hydroxypropyl cellulose, etc. The excipient may be used alone or in combination.

25

In addition, the composition according to the present invention may be prepared in the form of a granule, a powder or a dry syrup by masking the bitter taste by coating it with a water insoluble material or by adding an appropriate material. These formulations are also encompassed by the formulation of the present invention, but the present invention is not limited thereto.

30

EXAMPLES

The present invention will be described in greater detail through the following examples. The examples are presented for illustrating purposes only and should not be construed as limiting the invention which is properly delineated in the claims.

5

Example 1:

The following components were blended together, and compacted into granules with a roller compactor. The resulting granules were then compressed with a
10 conventional tableting machine.

15

Components	Contents (mg/tablet)
Cefuroxime axetil	the amount equivalent to 250.00 mg of Cefuroxime
Silicon dioxide	80.0
Low substituted hydroxypropyl cellulose	40.0
Sodium starch glycolate	150.0
Stearic acid	30.0

20 **Example 2**

The following components were blended together, and compacted into granules with a roller compactor. The resulting granules were then compressed with a conventional tableting machine.

25

Components	Contents (mg/tablet)
Cefuroxime axetil	the amount equivalent to 250.00 mg of Cefuroxime
Low substituted hydroxypropyl cellulose	40.0

- 13 -

Sodium starch glycolate	150.0
Stearic acid	30.0

5 Example 3

1. Capsule contents

The following components were blended together, and compacted into granules with a roller compactor. The resulting granules were then filled into a hard capsule

10 with a conventional capsule filler.

	Components	Contents (mg/capsule)
	Cefuroxime axetil	the amount equivalent to 250.00 mg of Cefuroxime
	Silicon dioxide	300.0
15	Low substituted hydroxypropyl cellulose	80.0
	Sodium starch glycolate	110.0
	Stearic acid	30.0

20 Example 4

1. Capsule contents

The following components were blended together, and compacted into granules with a roller compactor. The resulting granules were then filled into a hard capsule with a conventional capsule filler.

25

	Components	Contents (mg/capsule)
	Cefuroxime axetil	the amount equivalent to 250.00 mg of Cefuroxime
	Low substituted hydroxypropyl cellulose	80.0

- 14 -

Sodium starch glycolate	110.0
Stearic acid	30.0

5 Example 5

1. Tablet core

The following components were blended together, and compacted into granules with a roller compactor. The resulting granules were then compressed with a conventional tableting machine.

10

Components	Contents (mg/tablet)
Cefuroxime axetil	the amount equivalent to 250.00 mg of Cefuroxime
Silicon dioxide	80.0
Low substituted hydroxypropyl cellulose	80.0
15 Sodium starch glycolate	110.0
Stearic acid	30.0

2. Film forming composition

The tablet cores as prepared in the above step were applied to a conventional
20 pan coater and the film forming material having the following composition was sprayed
in a conventional manner to coat the tablets. The amount of the coating material was
adjusted to a range between 0.005 and 0.05 parts by weight based on the weight of the
tablet core.

25

Components	Added amount (%)
Eudragit L 30 D	16.6
Talc	4.0
Polyethylene glycol 6000	1.6
Purified water up to	100.0

Examples 6 to 14

Tablet cores and film forming compositions of Examples 6 to 14 were prepared according to the same manner as in Example 5 except for the components specified in 5 each example.

Example 6

1. Tablet core

10	Components	Contents (mg/tablet)
	Cefuroxime axetil	the amount equivalent to 250.00 mg of Cefuroxime
	Silicon dioxide	35.0
	Low substituted hydroxypropyl cellulose	80.0
	Sodium starch glycolate	155.0
	Polyethylene glycol 6000	30.0

15

2. Film forming composition

20	Components	Added amount (%)
	Eudragit L 30 D	16.6
	Talc	4.0
	Polyethylene glycol 6000	1.6
	Purified water up to	100.0

Example 7

1. Tablet core

25	Components	Contents (mg/tablet)
	Cefuroxime axetil	the amount equivalent to 250.00 mg of Cefuroxime
	Silicon dioxide	80.0

- 16 -

Low substituted hydroxypropyl cellulose	70.0
Polacrillin potassium	110.0
Stearic acid	30.0

5 2. Film forming composition

Components	Added amount (%)
Eudragit L 30 D	16.6
Talc	4.0
Purified water up to	100.0

10

Example 8

1. Tablet core

Components	Contents (mg/tablet)
Cefuroxime axetil	the amount equivalent to 250.00 mg of Cefuroxime
15 Silicon dioxide	105.0
Low substituted hydroxypropyl cellulose	70.0
Sodium starch glycolate	75.0
Polyethylene glycol 6000	20.0

20 2. Film forming composition

Components	Added amount (%)
Eudragit L 30 D	6.0
Talc	3.0
Triethyl citrate	0.6
25 Purified water	5.0
Isopropyl alcohol up to	100.0

Example 9

- 17 -

1. Tablet core

	Components	Contents (mg/tablet)
	Cefuroxime axetil	the amount equivalent to 250.00 mg of Cefuroxime
	Silicon dioxide monohydrate	125.0
5	Low substituted hydroxypropyl cellulose	90.0
	Sodium starch glycolate	60.0
	Magnesium Stearate	30.0

2. Film forming composition

10	Components	Added amount (%)
	Hydroxypropylmethylcellulose phthalate	5.0
	Triacetin	3.0
	Hydroxypropylmethyl cellulose	0.02
	Purified water up to	100.0

15

Example 10

1. Tablet core

	Components	Contents (mg/tablet)
	Cefuroxime axetil	the amount equivalent to 500.00 mg of Cefuroxime
20	Silicon dioxide monohydrate	210.0
	Low substituted hydroxypropyl cellulose	190.0
	Sodium starch glycolate	150.0
	Stearic acid	30.0

25 2. Film forming composition

	Components	Added amount (%)
	Eudragit L 30 D	16.6

- 18 -

Talc	4.0
Triacetin	1.6
Hydroxypropylmethyl cellulose	0.02
Purified water up to	100.0

5

Example 11

1. Tablet core

	Components	Contents (mg/tablet)
10	Cefuroxime axetil	the amount equivalent to 500.00 mg of Cefuroxime
	Silicon dioxide	160.0
	Low substituted hydroxypropyl cellulose	160.0
	Sodium starch glycolate	220.0
	Stearic acid	50.0

15

2. Film forming composition

	Components	Added amount (%)
	Hydroxypropylmethylcellulose phthalate	5.0
	Triacetin	3.0
20	Hydroxypropylmethyl cellulose	0.02
	Purified water up to	100.0

Example 12

25 1. Tablet core

	Components	Contents (mg/tablet)
	Cefuroxime axetil	the amount equivalent to 125.00 mg of Cefuroxime

- 19 -

Silicon dioxide	125.0
Low substituted hydroxypropyl cellulose	100.0
Sodium starch glycolate	90.0
Stearic acid	15.0

5

2. Film forming composition

Components	Added amount (%)
Eudragit L 30 D	16.6
Talc	4.0
Triacetin	1.6
Hydroxypropylmethyl cellulose	0.02
Purified water up to	100.0

10

15 **Example 13**

1. Tablet core

Components	Contents (mg/tablet)
Cefuroxime axetil	the amount equivalent to 125.00 mg of Cefuroxime
Silicon dioxide	40.0
Low substituted hydroxypropyl cellulose	40.0
Sodium starch glycolate	60.0
Stearic acid	15.0

20

2. Film forming composition

Components	Added amount (%)
Eudragit L 30 D	16.6
Talc	4.0
Triacetin	1.6

25

- 20 -

Hydroxypropylmethyl cellulose	0.02
Purified water up to	100.0

5 Example 14

1. Tablet core

	Components	Contents (mg/tablet)
	Cefuroxime axetil	the amount equivalent to 125.00 mg of Cefuroxime
	Silicon dioxide monohydrate	53.0
10	Low substituted hydroxypropyl cellulose	45.0
	Sodium starch glycolate	50.0
	Magnesium stearate	10.0

2. Film forming composition

15	Components	Added amount (%)
	Hydroxypropylmethylcellulose phthalate	5.0
	Triacetin	3.0
	Hydroxypropylmethyl cellulose	0.02
	Purified water up to	100.0

20

Experiment 1

In order to demonstrate the effect that silicon dioxide prevents cefuroxime axetil from being gelled, a dissolution test was conducted for the tablets according to Examples 1 and 2 in accordance with the method illustrated in the monograph of the cefuroxime axetil tablets of Vol. 23, on page 316 of the U.S. pharmacopeia. The results are shown in Fig. 1.

As can be seen from the Fig. 1, the tablet of Example 1 containing 80 mg of

- 21 -

silicon dioxide showed 87.2% of dissolution rate after 45 minutes while that of Example 2 which is devoid of silicon dioxide showed only 30.4% of dissolution rate and left undissolved small mass in dissolution medium. Therefore, it is noted that silicon dioxide is excellent in preventing gel formation of cefuroxime axetil.

5

Experiment 2

In order to demonstrate the effect that silicon dioxide prevents cefuroxime axetil from being gelled in the capsule preparation, a dissolution test was conducted for the capsules according to Examples 3 and 4 in accordance with the method illustrated in the monograph of the cefuroxime axetil tablets of Vol. 23, on page 316 of the U.S. pharmacopeia. The results are shown in Fig. 2.

As can be seen from the Fig. 2, the capsule of Example 3 containing 300 mg of silicon dioxide showed 84.3% of dissolution rate after 45 minutes while that of Example 4 which is devoid of silicon dioxide showed only 29.6% of dissolution rate. Therefore, it is noted that silicon dioxide in the capsule preparation is excellent in preventing gel formation of cefuroxime axetil.

Experiment 3

In order to determine the effect that silicon dioxide stabilize cefuroxime axetil, a tablet core of Example 5 was stored under the accelerated test condition. The test was carried out with naked tablets in order to exclude any effect of the film forming material on the stability of the tablet. The storage condition in the accelerated test was 40 °C and 75% of relative humidity. Upon storage of the tablet in open state for 30 days, the moisture content and dissolution rate were determined. The results are shown in Table 1.

Table 1

	Tablet core of Example 5	
	0	30
Storage time(day)		
Moisture contents	1.21 %	3.03 %

- 22 -

Content	99.39%	97.81%
---------	--------	--------

As can be seen from Table 1, it was found that even if the tablet core according to Example 5 was stored under the accelerated condition in the naked and opened state, the moisture content after 30 days was increased to 3.3% while only 1.58% of the content was changed (from 99.39% to 97.81%). Therefore, it is noted that the composition of the tablet core according to Example 5 has excellent stability even under the severe condition.

10 Experiment 4

In order to compare the tablet according to the present invention with that of the prior art, the tablet of the present invention in which a tablet core comprising effective amount of cefuroxime axetil and a specific amount of silicon dioxide was coated with the acidic film forming material (test preparation) and that of Example 3 of Korean Patent No. 73572 (comparative preparation) were subjected to dissolution test in accordance with the method illustrated in the monograph of the cefuroxime axetil tablets of Vol. 23, on page 316 of the U.S. pharmacopeia. The test preparation was the tablet according to Example 5 of the present invention and the comparative preparation was prepared as follows:

20

The tablet core of the comparative preparation was prepared according to Example 3 of Korean Patent No. 73572, except that titanium dioxide was used in stead of Opaspray Blue M-1-4395B in the film forming composition in Example 3. The components employed were set forth in the following tables. Opaspray, which is based on titanium dioxide with lake colors, is presumed to give a sunscreen effect and to reveal a color. This pigment is known to commercially available from Colorcon Ltd. at Orpington of Kent, United Kingdom. However, since it was difficult to purchase the product and to find out the exact composition thereof, the inventors used titanium dioxide. When titanium dioxide was only added into the film forming composition in lieu of opaspray blue M-1-4395B, it was observed that the rupture time of the film in the solution of 0.07 M of hydrochloric acid was below 40 seconds, exactly less than 10 seconds. The rupture time was measured as the time which elapses before the core of

the tablet first become visible to the naked eye through the ruptured film coat. Therefore, it was confirmed that the substitution of the pigment did not influence any effect on the dissolution rate of the tablet according to Example 3 of Korean Patent No. 73572.

5

1. Tablet core

The following components except for silicon dioxide were blended together, and compacted with a roller compactor. The compacted materials were comminuted with an oscillating granulator and the resulting granules were blended with silicon dioxide,
10 and were then the compressed with a conventional tableting machine.

	Components	Contents (mg/tablet)
	Cefuroxime axetil	the amount equivalent to 250.00 mg of Cefuroxime
	Microcrystalline cellulose	94.55
15	Croscarmellose sodium Type A	15.50
	Sodium lauryl sulphate	4.50
	Silicon dioxide	1.25
	Hydrogenated vegetable oil	8.50

20 2. Film forming composition

The tablet cores as prepared in the above step were put into a conventional pan coater and the film forming material having the following composition was sprayed in the conventional manner to coat the tablets. The tablet was coated with a target coat weight of 1 mg per 32 mm².

25

Components	Added amount (%)
Hydroxypropylmethylcellulose 6	10.0
Propylene glycol	0.60
Methyl hydroxybenzoate	0.10

Propyl hydroxybenzoate	0.08
Titanium dioxide	10.00
Purified water up to	100.0

- 5 The dissolution rate results were set forth in figure 3. As can be seen from the Fig. 3, the test preparation according to the invention showed 91% of dissolution rate after 45 minutes while the comparative preparation showed only 35%. Therefore, it was found that the test preparation is superior to the comparative preparation in the dissolution rate.

10

Experiment 5

- Each 250 mg of the coated tablet of Example 5 and the commercial cefuroxime axetil tablet (available from Glaxo Wellcome P.L.C.) were stored under the accelerated test condition and subjected to the content test and dissolution rate test in accordance with the method illustrated in the monograph of the cefuroxime axetil tablets of vol. 23, on page 316 of the U.S. Pharmacopeia. The storage condition in the accelerated test was 40 °C and 75% of relative humidity. After storing the coated tablet of Example 5 and the commercial product under the above condition in an opened state for 30 days, the content change and dissolution rate test were compared. The results are shown in Fig. 4 and Tables 2 and 3.

20

Table 2

25

		Commercial product		Tablet of Example 5	
Storage time(day)		0	30	0	30
Dissolution rate	15 min.	66.77	66.47	78.86	75.76
	45 min.	91.16	81.94	91.20	90.84
Reduced amount*		9.22		0.36	

Reduced amount*: Reduced amount of the drug dissolved at 45 min. during

- 25 -

the storage period(0-30 days)

Table 3

	Commercial product		Tablet of Example 5	
5 Storage time(day)	0	30	0	30
Contents	99.65	97.63	99.78	99.45
Decreased amount*	2.02		0.33	

Decreased amount*: Decreased amount of content in the product during the
10 storage period

As can be seen from the Fig. 4 and the above Tables 2 and 3 which reveal the changes in contents and dissolution rates before and 30 days after storage under the accelerated condition, the dissolution rate of the commercial product at 45 minute was
15 decreased by 9.22% after storing 30 days while that of the present invention (Example 5) was decreased by only 0.36%. As can be seen from Table 3, the contents of the cefuroxime axetil in the commercial product after 30 days was decreased by 2.02% while that of the present invention was decreased by only 0.33%. From the above results, the coated tablet according to the present invention shows excellent stability in
20 the dissolution rate and the contents, and thus, the tablet according to the invention is much more stable than the commercial product.

INDUSTRIAL APPLICABILITY

25 As can be seen from the above Experiments 1 to 5, the composition according to the present invention is characterized in that it comprises cefuroxime axetil and silicon dioxide or its hydrate as a micro-environmental pH adjustor and an anti-gelling agent for cefuroxime axetil can prevent the degradation or gel formation of the cefuroxime axetil due to the absorption of moisture in air upon long term storage and
30 make it possible to increase the dissolution rate of cefuroxime axetil regardless of the disintegration rate of the preparation containing cefuroxime axetil, thereby improving

- 26 -

the bioavailability. In Korean Patent No. 73572, it is only possible to avoid gel formation of cefuroxime axetil by providing specific tablet comprising a film which should be rapidly ruptured in an aqueous hydrochloric acid solution and a tablet core which is disintegrated immediately after the film is ruptured. However, according to the
5 present invention, the gel formation of cefuroxime axetil in oral formulation in the form of tablet, capsule, granule, powder and dry syrup is prevented and an excellent dissolution rate is obtained.

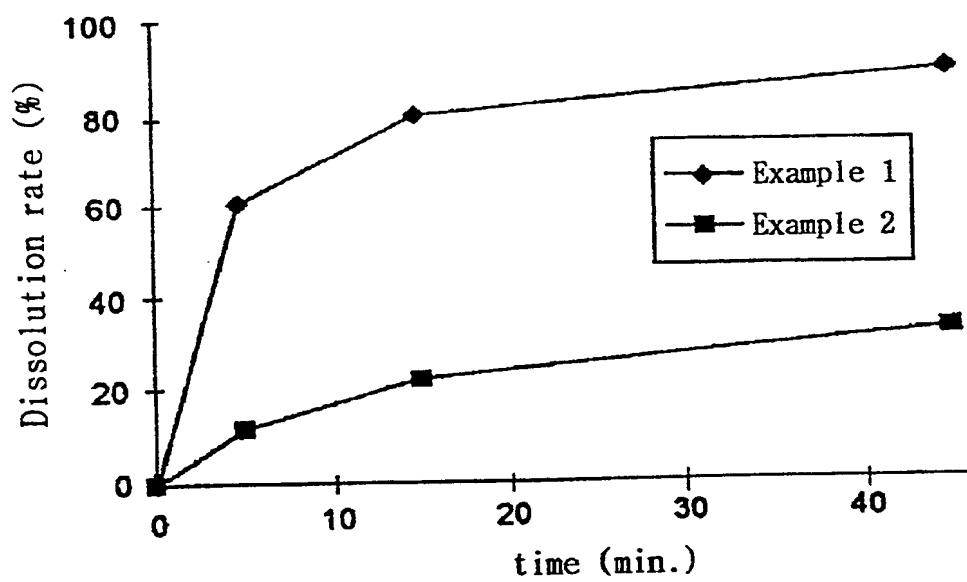
- 27 -

CLAIMS

1. A pharmaceutical composition which comprises amorphous cefuroxime axetil as an active ingredient and silicon dioxide or its hydrate as a micro-environmental pH adjustor around cefuroxime axetil and an anti-gelling agent for cefuroxime axetil.
2. The composition of Claim 1, wherein the weight ratio of cefuroxime axetil and silicon dioxide or its hydrate is 1:0.1 to 1:1.
3. The composition of Claim 1, wherein the weight ratio of cefuroxime axetil and silicon dioxide or its hydrate is 1:0.25 to 1:0.35.
4. The composition of Claim 1 in the form of an oral formulation selected from the group consisting of tablets, capsules, granules, powders and dry syrups.
5. The composition of Claim 4 in the form of tablet or capsule formulation wherein cefuroxime axetil and silicon dioxide or its hydrate are contained in an amount of 16 to 90 % by weight based on the total amount of the formulation.
6. The composition of Claim 5 in the form of tablet wherein a tablet core containing amorphous cefuroxime axetil as an active ingredient, silicon dioxide or its hydrate and pharmaceutically acceptable excipients is film-coated with the film forming material comprising acidic polymeric material(s).
7. The composition of Claim 6, wherein the acidic polymeric material is selected from the group consisting of methacrylic copolymer, hydroxypropylmethylcellulose phthalate, celluloseacetate phthalate and hydroxypropylmethylcellulose acetate succinate, and a mixture thereof.

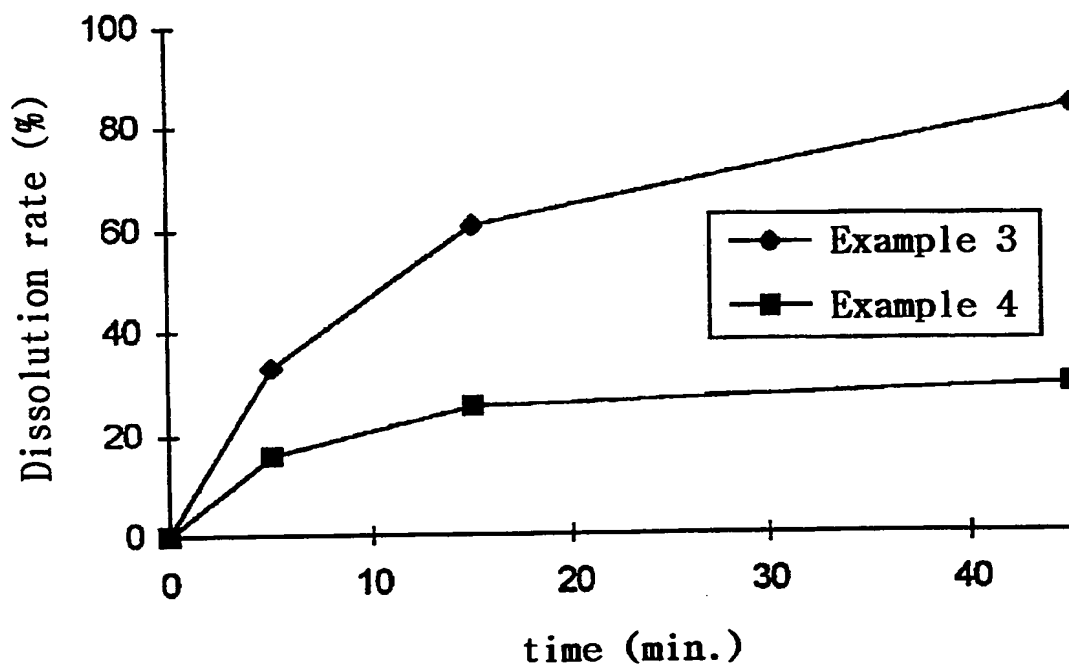
1/4

Fig. 1



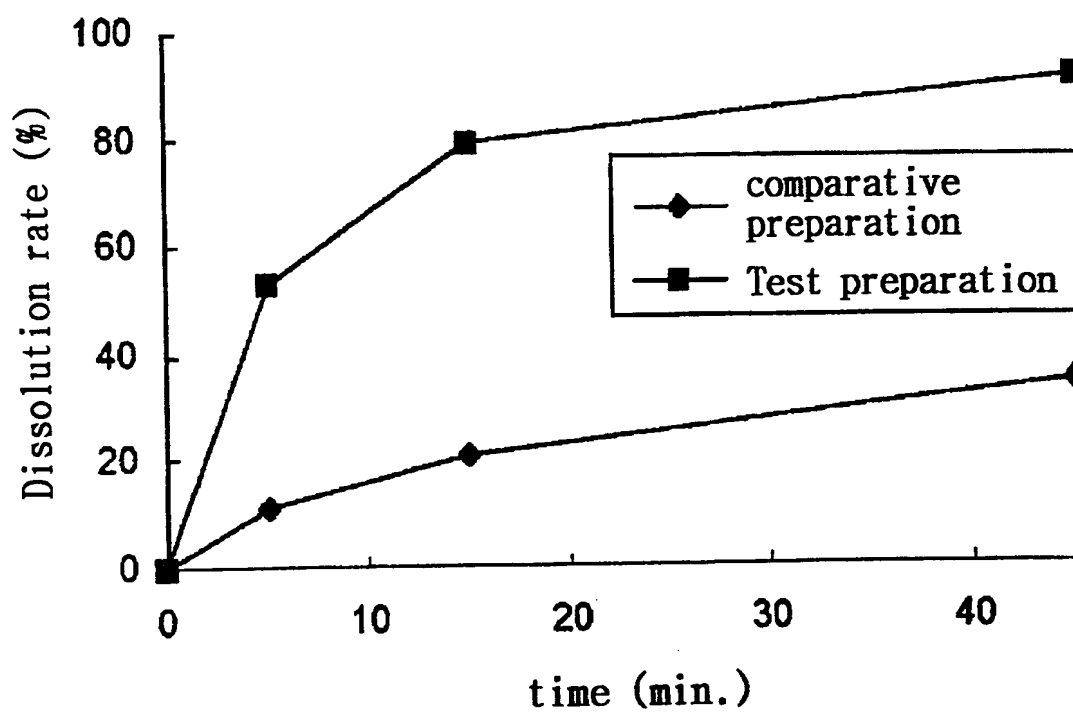
2/4

Fig. 2



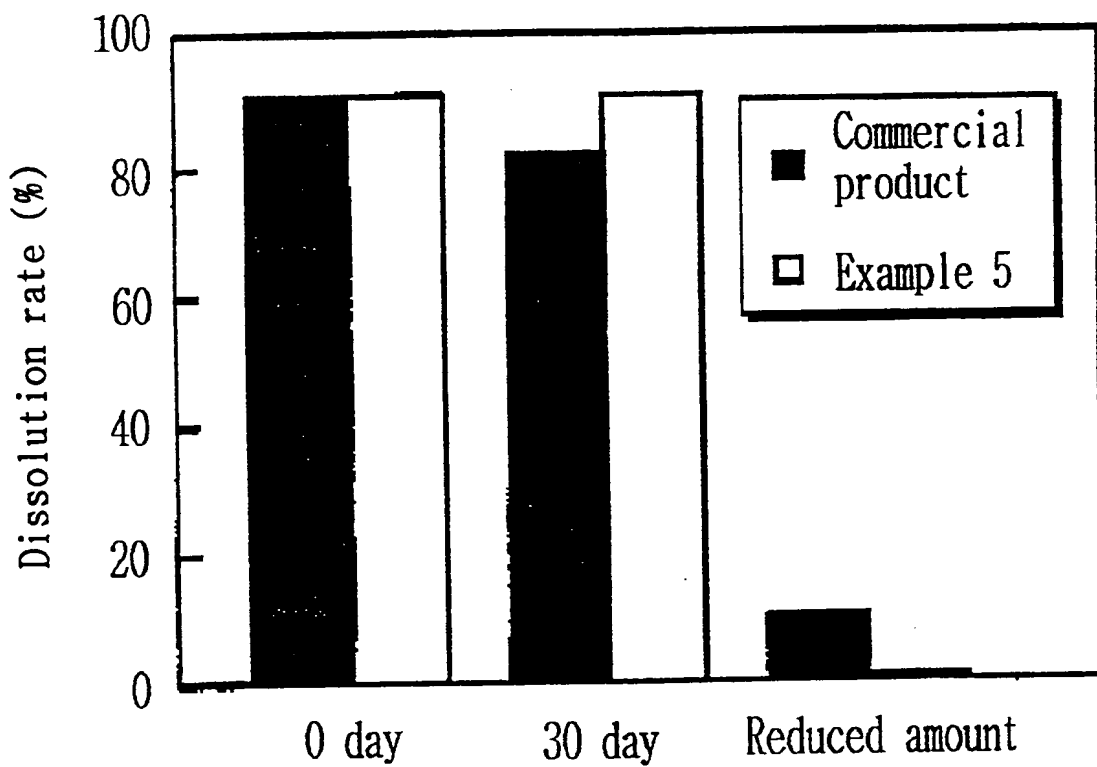
3/4

Fig. 3



4/4

Fig. 4



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00095

A. CLASSIFICATION OF SUBJECT MATTER

IPC⁶: A 61 K 31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁶: A 61 K 31/545

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

QUESTEL: WPIL, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 127 401 A (GLAXO GROUP LIMITED) 11 April 1984 (11.04.84), claim 21; page 3, lines 47-63; page 8, pharmacy examples 1,2 (cited in the application).	1,4
X	GB 2 181 052 A (GLAXO GROUP LIMITED) 15 April 1987 (15.04.87), abstract; claims 1,15-18; examples 1-4.	1,4,6,7
A	EP 0 280 571 A2 (ELI LILLY AND COMPANY) 31 August 1988 (31.08.88), claims 1,3; page 4, lines 8-25.	1,4,6,7

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

„A“ document defining the general state of the art which is not considered to be of particular relevance

„E“ earlier application or patent but published on or after the international filing date

„L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

„O“ document referring to an oral disclosure, use, exhibition or other means

„P“ document published prior to the international filing date but later than the priority date claimed

„T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

„X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

„Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

„&“ document member of the same patent family

Date of the actual completion of the international search

14 April 1999 (14.04.99)

Date of mailing of the international search report

21 June 1999 (21.06.99)

Name and mailing address of the ISA/AT
Austrian Patent Office
Kohlmarkt 8-10; A-1014 Vienna
Facsimile No. 1/53424/200

Authorized officer

Mazzucco

Telephone No. 1/53424/437

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/KR 99/00095

la Recherchebericht angeführtes Patentdokument in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
GB A	21274	AT A 2767/83	15-06-1986
		AT B 382154	26-01-1987
		AU A1 17417/83	02-02-1984
		AU B2 566881	05-11-1987
		BE A1 897422	30-01-1984
		CA A1 1240313	09-08-1988
		CH A 657134	15-08-1986
		CS A2 8305687	15-03-1988
		CS B2 259515	14-10-1988
		CY A 1434	02-09-1988
		CZ A3 9104031	12-05-1993
		CZ B6 280528	14-02-1992
		DE A1 3327449	02-02-1984
		DE C0 3374010	12-11-1987
		DK A0 3490/83	25-07-1983
		DK A 3490/83	31-01-1984
		DK A 683/92	25-05-1992
		DK A0 683/92	25-05-1992
		DK B 164507	06-07-1992
		DK C 164507	23-11-1992
		EP A2 107276	02-05-1984
		EP A3 107276	06-03-1985
		EP B1 107276	07-10-1987
		ES A1 524590	01-06-1985
		ES A5 524590	28-06-1985
		ES A1 8505689	01-10-1985
		FI A0 832757	29-07-1983
		FI A 832757	31-01-1984
		FI B 76093	31-05-1988
		FI C 76093	09-09-1988
		FR A1 2531087	03-02-1984
		FR B1 2531087	22-11-1985
		GB A0 8320518	01-09-1983
		GB A1 2127401	11-04-1984
		GB B2 2127401	16-04-1986
		GR A 79349	22-10-1984
		HK A 842/88	28-10-1988
		HU B 190603	29-09-1986
		IE B 55748	02-01-1991
		IL A0 69375	30-11-1983
		IL A1 69375	31-12-1986
		IT A0 8348789	29-07-1983
		IT A 1168206	20-05-1987
		JP A2 59044391	12-03-1984
		JP B4 7030084	05-04-1995
		KE A 3805	03-06-1988
		KR B1 9100046	19-01-1991
		LU A 84935	23-11-1983
		MY A 58/87	31-12-1987
		NL A 8302705	16-02-1984
		NO A 832773	31-01-1984
		NO B 163897	30-04-1990
		NO C 163897	08-08-1990
		NZ A 205083	14-03-1986
		PL A1 243228	27-08-1984
		PL B1 156001	31-01-1993
		PT A 77135	01-08-1983
		PT B 77135	24-01-1986
		SE A0 8304208	29-07-1983
		SE A 8304208	31-01-1984
		SE B 453195	18-01-1988
		SE C 453195	28-04-1988
		SG A 260/88	15-07-1988
		SI A8 8311558	31-12-1993
		SK A3 4031/91	11-07-1993
		SK B6 277896	11-07-1993
		SU A3 1266471	23-10-1986
		US A 4562181	31-12-1985
		US A 4820833	11-04-1989
		US A 4994567	19-02-1991
		US A 5013833	07-05-1991
		YU A 1558/83	30-04-1986
		YU B 44680	31-12-1990
		ZA A 8305579	26-09-1984
		ZW A 173/83	26-10-1983

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR 99/00095

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
GB A	21274	AT A 2767/83	15-06-1986
		AT B 382154	26-01-1987
		AU A1 17417/83	02-02-1984
		AU B2 566881	05-11-1987
		BE A1 897422	30-01-1984
		CA A1 1240313	09-08-1988
		CH A 657134	15-08-1986
		CS A2 8305687	15-03-1988
		CS B2 259515	14-10-1988
		CY A 1434	02-09-1988
		CZ A3 9104031	12-05-1993
		CZ B6 280528	14-02-1996
		DE A1 3327449	02-02-1984
		DE C0 3374010	12-11-1987
		DK A0 3490/83	25-07-1983
		DK A 3490/83	31-01-1984
		DK A 683/92	25-05-1992
		DK A0 683/92	25-05-1992
		DK B 164507	06-07-1992
		DK C 164507	23-11-1992
		EP A2 107276	02-05-1984
		EP A3 107276	06-03-1985
		EP B1 107276	07-10-1987
		ES A1 524590	01-06-1985
		ES A5 524590	28-06-1985
		ES A1 8505689	01-10-1985
		FI A0 832757	29-07-1983
		FI A 832757	31-01-1984
		FI B 76093	31-05-1988
		FI C 76093	09-09-1988
		FR A1 2531087	03-02-1984
		FR B1 2531087	22-11-1985
		GB A0 8320518	01-09-1983
		GB A1 2127401	11-04-1984
		GB B2 2127401	16-04-1986
		GR A 79349	22-10-1984
		HK A 842/88	28-10-1988
		HU B 190603	29-09-1986
		IE B 55748	02-01-1991
		IL A0 69375	30-11-1983
		IL A1 69375	31-12-1986
		IT A0 8348789	29-07-1983
		IT A 1168206	20-05-1987
		JP A2 59044391	12-03-1984
		JP B4 7030084	05-04-1995
		KE A 3805	03-06-1988
		KR B1 9100046	19-01-1991
		LU A 84935	23-11-1983
		MY A 58/87	31-12-1987
		NL A 8302705	16-02-1984
		NO A 832773	31-01-1984
		NO B 163897	30-04-1990
		NO C 163897	08-08-1990
		NZ A 205083	14-03-1986
		PL A1 243228	27-08-1984
		PL B1 156001	31-01-1992
		PT A 77135	01-08-1983
		PT B 77135	24-01-1986
		SE A0 8304208	29-07-1983
		SE A 8304208	31-01-1984
		SE E 453195	18-01-1988
		SE C 453195	28-04-1988
		SG A 260/88	15-07-1988
		SI A8 8311558	31-12-1993
		SK A3 4031/91	11-07-1995
		SK B6 277896	11-07-1995
		SU A3 1266471	23-10-1986
		US A 4562181	31-12-1983
		US A 4820833	11-04-1989
		US A 4994567	19-02-1991
		US A 5013833	07-05-1991
		YU A 1558/83	30-04-1986
		YU B 44680	31-12-1990
		ZA A 8305579	26-09-1984
		ZW A 173/83	26-10-1983